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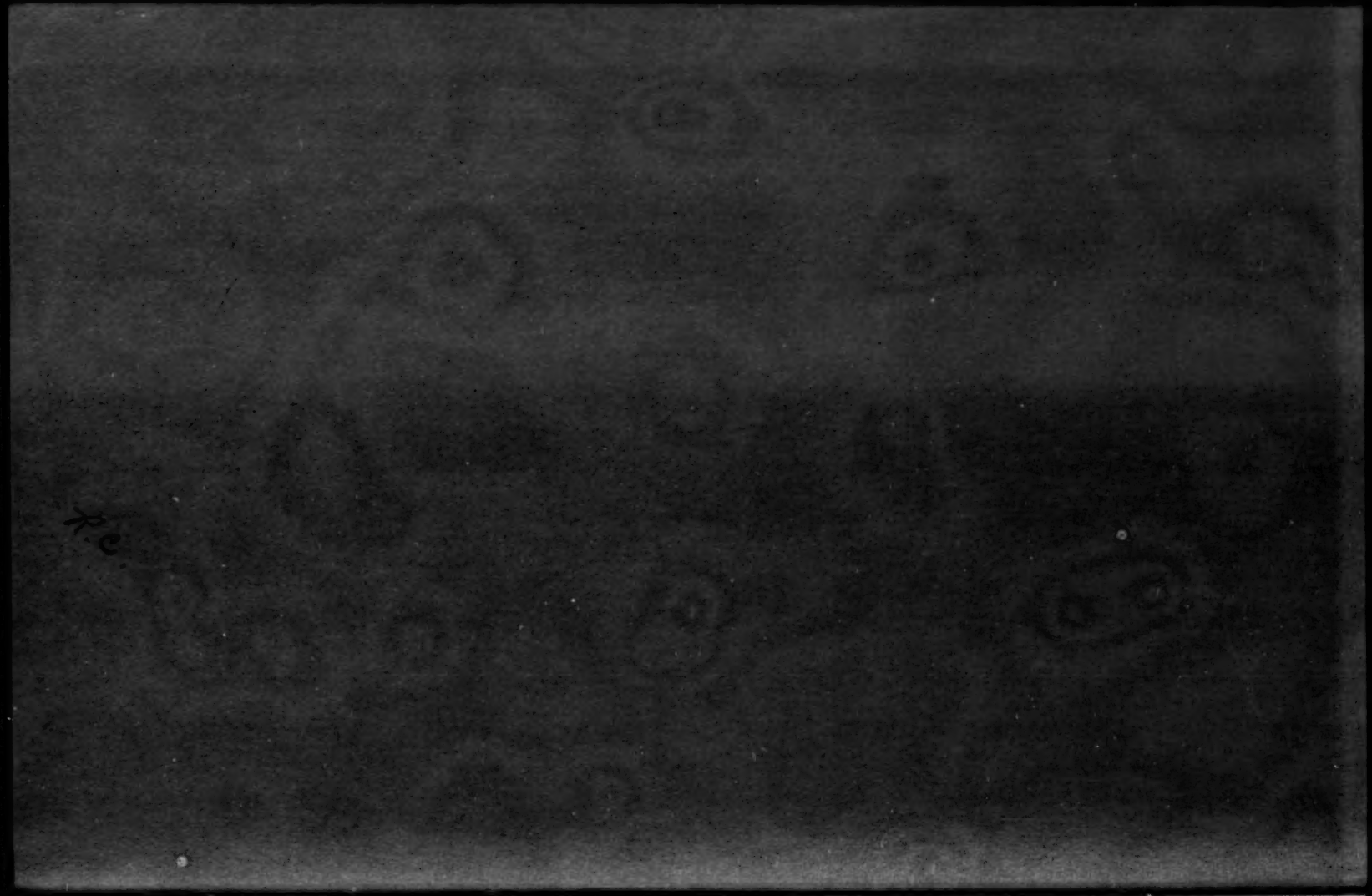

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY 1938

EDITORIAL ANNOUNCEMENT

THE Members and Fellows of the Academy, acting through their Council and Trustees, decided some time since on changing to some extent the nature of the BULLETIN. To this end a Board of Editors was appointed. For several years every function which the BULLETIN can serve has been carefully canvassed. As the result of many discussions and much planning, the BULLETIN appears in the first number of this new volume in a new dress. The new format is intended to symbolize the change, or the hope of change, which the BULLETIN is to undergo.

There is every reason to believe that the BULLETIN can be made to serve as the medium for reflecting the intellectual life and the activities of the Academy. Now, when the activities of the Academy have multiplied and its life has become richer, the need for developing its opportunities for publication have become apparent. Beside the Stated Meetings and the Section Meetings which constitute the backbone of its being, the Academy has affiliated with itself a number of cooperating scientific societies: the New York Roentgen Society, the Harvey Society, the Society for Experimental Biology and Medicine, and the New York Pathological Society. It provides, furthermore, series of lectures and discussions in many directions. The Annual Graduate Fortnight has become the occasion for presenting full reviews of subjects of active contemporary concern. It has come to engage the attention of large numbers of physicians in New York and elsewhere in the country. The

Academy houses the second largest collection of books of interest to medicine in the country, adding constantly to it whatever contributes to variety and value in medical learning. These large and varied activities give, and have given occasion for continuous meetings of physicians-practitioners and investigators—who in their reports and discussions provide a source whence flows a rich stream of learning and practical experience. The writings which come into being under these circumstances constitute the proper material for publication in the BULLETIN. Besides, accounts of the formal activities of the Academy will be suitably presented.

The Board of Editors will welcome especially reports of original researches undertaken by Members and Fellows of the Academy and by others wishing to use the good offices of the BULLETIN.

By following this plan, the usefulness of the BULLETIN will be much increased. From time to time editorial comments will appear, proposing, criticizing, appraising issues predominantly of scholarly interest, whether in the field of practice, administration or research. It is the intention in short to make of the BULLETIN a forum for discussion, on a high intellectual level, of matters having importance in the scientific and practical aspects of the life of medicine.

The Board of Editors is deeply indebted to Mr. David Silve for the imaginative quality he has displayed, for his understanding of the problems at issue, and the care with which he has planned this format; and to Mr. Charles C. Morchand, its publisher and printer, for his interest, his cooperative spirit and his unremitting unselfishness in bringing the new BULLETIN into existence. No detail has been too trivial to escape notice—the design of the cover; the several types of pages each appropriate to their subject matter; the typography; the selection of the paper on which can be reproduced all the usual forms of illustration; the form for references to scientific contributions and accessions to the library—all have been given due study. Especial attention is directed to the escutcheon designed by Dr. Dickinson, incorporated in the decorative border of the cover and printed in a different form on the opening page. The opportunity to utilize this forceful design in the scheme has contributed greatly to its success.

In this new dress the Board of Editors commends the BULLETIN afresh to the Members and Fellows of the Academy. It reminds them that on their active cooperation, the future of the BULLETIN must depend.

PHYSIOLOGY OF THE KIDNEY

*The Wesley M. Carpenter Lecture**

ALFRED N. RICHARDS

Professor of Pharmacology, University of Pennsylvania

THE KIDNEY is chief pathway of exit from the body of water and of non-volatile diffusible constituents of the blood. Its function, broadly considered, is the maintenance of that constancy of composition of the internal fluid environment of the cells of the body which is essential not only for health but for survival. It shares this function with the respiratory system, the skin, the gastro-intestinal tract. It accomplishes its function by the elimination of urine, at widely varying rates and of widely varying composition. Some of the diffusible constituents of plasma appear in the urine in concentrations far higher than those which obtain in the blood; some appear in urine in scarcely detectable traces. It seems as though the kidney can excrete urine of almost any composition which the internal environment of the body requires (Adolph).

The remarkable constancy of the composition of blood plasma, maintained against the assaults of periodic intake of varied amounts of fluid, salts and food, of changing external conditions, of widely differing metabolic activities, constitutes proof in itself of the flexible adaptability of the kidney, not only to the ever present demands of the body for the excretion of useless or deleterious substances, but also of its adaptability to the constant need of the body for protection against loss of vitally important substances. The conserving capacities of the kidney, responsible for the retention of water, of inorganic bases essential for the preservation of the electrolyte balance of the blood and for the retention of diffusible food stuffs are quite as necessary for preservation of the constant state as is its capacity to excrete metabolic waste, unneeded salts and water, foreign substances occasionally introduced.

The capacity of the kidney to deal individually with each of a multiplicity of substances with discriminating effectiveness provides

* Delivered November 1, 1937, in the Tenth Annual Graduate Fortnight

intricate problems both in the integrative physiology of the body as a whole and in cell or organ physiology which are of fundamental importance. The literature contains voluminous accounts of experimental researches, the purposes of which have been to describe the range of activities of the kidney in terms of its response to changes in its mass, to changes in its blood supply or innervation and particularly to changes in the composition of the blood from which its product is elaborated. A mass of important information has resulted, useful to physiology and to medicine, which shows, for example, the magnitude of the factor of safety in the renal structures (normal renal function can continue after half or more than half of the normal structure is removed); the changes in function which result from changes in its circulation (the vascularity of the kidney is so great that as much as one-fourth of the total blood in the body may traverse the renal vessels every minute); the fact that apparently normal renal function is not dependent upon an extrinsic nerve supply. It reveals the remarkable rapidity with which many foreign substances are excreted and it has shown the quality and quantity of the responses which the kidney makes to excess or deprivation of water, salts, acid, alkali, urea, etc.

Such studies define the usefulness of the kidney as the excretory servant of the body. Out of them have come tests of kidney function, methods of recognizing disorder of the kidney and evaluating its extent and probable outcome. They yield little information however which identifies or defines the individual processes by which urine is formed and elaborated within the kidney. They have given us hypotheses only with which to relate excretory or conservatory processes with the different parts of the renal apparatus. The physiologist and the physician hope ultimately to know what processes are operative in the different parts of the renal unit, the nephron, what controlling circumstances govern their activities, how they are coordinated, not only within a single unit or among the myriads of units which constitute the kidney but how the mass activity of the whole organ is coordinated in such a way as to serve the body with such remarkable efficiency.

My working interests for many years past have expressed themselves in attempts to design experiments which might clarify my understanding of the nature and site of processes of urine formation within the kidney: much of what I shall now have to say will represent the results of such attempts.

It seems almost obligatory to begin this discussion with allusions to the work of great predecessors in the past out of which present knowledge has developed.

Bellini is said to have been the first to publish a description of the renal tubules in 1662. In 1666 Malpighi described the globular structures in the cortex which at once became known as the Malpighian bodies. He showed that they were connected with the arteries and guessed, but could not demonstrate, that they were connected with the tubules. Nearly two centuries elapsed before Bowman, a 26-year-old demonstrator of anatomy in London, proved by beautiful dissections that the Malpighian body is the expanded end—the beginning—of the renal tubule; that the intracapsular space is continuous with the lumen of the tubule. Impressed by the resemblance of the tubules to the acini of digestive glands, he conceived that the cells which compose their walls secrete the waste products of metabolism from blood into their lumina; the glomerular capillaries seemed to him peculiarly suited to permit the escape of water from the blood. From these two impressions he constructed the hypothesis that the urinous constituents of blood are secreted by the tubule cells and washed out of the lumen by a saline stream flowing down from the glomerulus.

Bowman's discovery was at once confirmed by another youngster of his own age and of comparable genius, Carl Ludwig. He examined the structures with the eyes of a physiologist whose ambition it was to interpret vital phenomena in terms of physics and chemistry. He saw the hydrodynamic possibilities of the arrangement of glomerular capillaries and boldly stated that this structure must be a filter; that the beginnings of urine formation consist in the separation of a cell-free, protein-free filtrate from the blood as it passes through the glomerular capillaries, in volume sufficient to contain all of the dissolved components of urine; that this filtrate in its passage down the tubule is concentrated by reabsorption from the tubule and issues into the pelvis of the kidney reduced in volume, increased in concentration, fully elaborated urine.

The significance of the work of these two young men can scarcely be overestimated. In the space of two years (1842-'44) physiology was supplied with a correct structural representation of the unit of kidney function and with two hypothetical conceptions of processes operative within it. A great part of subsequent experimental study has been influenced by these concepts and the results expressed in their terms.

During the following years experiments instigated by Ludwig, which showed the relations between changes in rate of urine output on the one hand and changes in arterial blood pressure or in ureteral pressure on the other, yielded results which were in harmony with his filtration-reabsorption theory. These, together with the influence of Ludwig, resulted in widespread acceptance of Ludwig's ideas. But in the years 1874-1883 work by Heidenhain of Breslau upset this view. He found that the diffusible dye, indigo carmine, injected intravenously into rabbits, is rapidly excreted in the urine in high concentration but is not detectable in the glomerular capsules seen in sections of the kidney, excised while excreting it. Hence he concluded that indigo carmine is not excreted through the glomerulus. It is a diffusible substance; therefore the glomerulus is not a filter but a secreting structure with the capacity of selecting what shall pass through it.

He reduced the blood pressure in rabbits by section of the spinal cord to a level which abolished urine elimination. Then, having injected indigo carmine, he excised the kidney, found massive accumulations of dye in the lumina of tubules, concluded that it could have found access to them only through the cells of the tubules; hence these are secreting cells.

He raised glomerular capillary blood pressure, not as Ludwig had done, by increasing arterial blood pressure, which also increases rate of blood flow, but by partially obstructing the renal vein, which decreases blood flow. He found that rate of urine flow always diminished. From this he argued that rate of blood flow through the glomerular capillaries rather than the blood pressure within them is the prime essential in the production of glomerular urine. It acts, he thought, by altering the state of nutrition of the epithelium which covers those capillaries.

He calculated the volume of filtrate from blood plasma which would be required to contain the amount of urea which a man excretes in a day. The figure arrived at was 70 litres: of this, according to the filtration theory, some 68 litres must be reabsorbed if the day's output of urine were 2 litres. He did not believe that a volume of blood sufficient to yield 70 litres of filtrate flows through the kidneys in a day: he regarded such an uneconomical process as his figures indicated as incredible.

These facts and arguments and the skill with which they were presented caused physiologists throughout the world to recant their

faith in Ludwig; and for the next thirty years the physiology of the kidney was principally taught in terms of the Bowman-Heidenhain secretory theory.

The literature of that period is a literature of debate. Neither the concept of filtration-reabsorption nor that of secretion could satisfactorily answer the objections of the one against the other. Experiments which compelled belief were lacking.

Between 1896 and 1917 work was published which had the effect of slowly reinstating the filtration doctrine in the respect of physiology. Of outstanding importance was Starling's classical demonstration of the osmotic pressure of plasma proteins, previously thought, because of the great size of their molecules, to be osmotically inert. He showed that their osmotic pressure amounts to some 30 mm. Hg, i.e., when plasma is separated from isotonic saline by a membrane impermeable to protein but permeable to water and salt, fluid is drawn in to the plasma with an initial force of 30 mm.; or if the attempt is made to filter plasma through a membrane impermeable to its proteins, a pressure greater than 30 mm. Hg must be applied before any protein-free fluid can separate.

Starling then found that in diuretic dogs, urine formation ceases when arterial blood pressure is reduced to about 40 mm.; that when the ureter is obstructed, urine continues to be formed until the ureteral pressure has risen to a level about 40 mm. of mercury below that of the arterial pressure. The coincidence of these two values, and the fact that they approximated so closely to his values of the colloid osmotic pressure of plasma led him to think that the plasma proteins interposed an obstacle to the formation of urine of the same sort as that which they interpose to filtration through a membrane; in a word, that a process of filtration is concerned in urine formation.

Experiments by Bainbridge showed that whereas normal frog's urine is strongly hypotonic to plasma, when the tubules (but not the glomeruli) are poisoned with bichloride of mercury, the urine becomes isotonic. His inference was that the glomerular urine is a filtrate which is rendered hypotonic by reabsorptive processes in the tubule.

Another important influence was the publication in 1917 of a monograph on the Secretion of Urine by Cushny. He made an exceedingly thorough critical analysis of existing experimental evidence which, while it exposed the deficiencies of the evidence for both theories, revealed greater weaknesses in the basis of the secretion doctrine than in that

of filtration-reabsorption. From this analysis Cushny developed a modification of Ludwig's ideas which he termed the Modern Theory and which found widespread acceptance.

Thus, some twenty years ago, physiology found itself in possession of hypothetical concepts of renal function, of an enormous mass of experimentally acquired information bearing upon these, but still unable, with decisive certainty, to answer some of the simplest, most direct questions which had been confronting her from the moment when the true relationship between glomerulus and tubule was discovered.

Does the glomerulus play a passive or an active role in urine formation? What is the extent of its participation? Do the tubule cells secrete material from blood to lumen of tubule or do they secrete constituents of the glomerular product back into the blood from the lumen of the tubule; or do they do both? Is there a division of function in the different, structurally unlike parts of the tubule?

These are precisely the questions which troubled Bowman, Ludwig, Heidenhain, Starling and Cushny: they are still of great concern to us, though distinct progress has, I think, been made toward their solution in the past twenty years; it is of this progress which I now wish to speak.

First concerning the nature of glomerular function.

If we knew with certainty the differences between the composition of the plasma of the blood flowing through the glomerular capillaries and that of the fluid which separates from it at that point, we should know at once whether the glomerular membrane behaves like a filter or whether it exhibits capacities of retarding or of accelerating the passage of individual components of the plasma through it. If in addition we knew the volume of this separated fluid which is delivered into the tubules we should be able at once to define the task of the tubules, at least in general terms.

In the autumn of 1921 workers in my laboratory found themselves in possession of two techniques which had not previously been used in the study of the kidney, both adaptations of methods used in other connections by other workers. One was a method of microscopic observation of the frog's kidney during life, similar in design and purpose to that which Krogh had utilized in his studies of capillaries; indeed to that which, long ago, Malpighi had used in his discovery of the capillary connections between arteries and veins. The other was a micro-dissection method, a somewhat crude though effective modification of that which I

had seen Robert Chambers using in his manipulations of single cells, by which it was possible to insert sharply pointed tubes into the space within Bowman's capsule and to abstract the fluid which issues from the blood of the glomerular capillaries. The amounts of fluid thus obtainable were small—usually less than 0.001 cc.—but it was easily possible to submit them to simple qualitative chemical tests, conducted in capillary tubes. The results showed that the glomerular fluid is free from protein but contains chloride and glucose, both of these being absent from bladder urine. It is alkaline, contains urea, and indeed every diffusible constituent of plasma for which we were able to make a test.

With time and patience it became possible to adapt to these small quantities of fluid a number of quantitative methods for the determination of individual constituents with highly satisfactory accuracy, and as a result we now have a fair number of quantitative comparisons of the concentrations of individual plasma solutes in glomerular urine and in plasma of frogs and Necturi, simultaneously collected from the same animal.

The results show that glomerular urine collected both from frogs and Necturi has the same composition as a plasma ultrafiltrate with respect to total concentration of solutes (vapor pressure), total electrolytes (electrical conductivity), pH, chlorides, inorganic phosphates, glucose, urea, uric acid, creatinine, phenol red, indigo carmine and inulin. The last five substances were injected subcutaneously or intravenously before beginning the collection of glomerular urine.

These results seem to me to leave little room for doubt that, in amphibia, the glomerular urine actually has the composition of a protein-free filtrate from plasma, precisely as Ludwig had imagined ninety-three years ago. They show that, so far as the frog is concerned, Heidenhain was wrong in denying that indigo carmine escapes from the blood through the glomerular membrane. They give no evidence that the glomerulus possesses any capacity whatever of selecting what substances shall or shall not pass through it if only they are diffusible.

I call particular attention to the fact that the results with inulin are wholly similar to the rest. This is a polysaccharide of high molecular weight (5100), consisting of some 32 levulose groups probably put together in the form of a chain. Its diffusibility through membranes is much slower than is that of urea, glucose or NaCl: in free diffusion experiments (i.e., conducted with no membrane) its mobility corre-

sponds to that of a spherical molecule of 15,000 molecular weight (Bunim and Smith). The fact that this large and slowly moving molecule passes through the glomerular membrane at the same rate as does that of urea, which is only 1/85 as heavy and far more mobile, yields two conclusions: one, that the passages or pores through the membrane are far larger than is necessary for the escape of the normal, diffusible constituents of plasma. The membrane is a relatively wide-meshed sieve. Another, that diffusion plays no significant part in determining the composition of glomerular urine as I am sure it does in determining that of fluid separated from blood in the systemic capillaries.

Another important piece of cognate information was obtained by Hayman. He succeeded in measuring the blood pressure in the capillaries of a single glomerulus by an application of the principle of the Riva-Rocci sphygmomanometer. He closed the neck of the tubule; through a capillary pipette in the capsular space raised the pressure within Bowman's capsule to a height at which corpuscles were seen to be flowing through only two or three of the capillary loops instead of all the six which they usually contain and found that on the average, the glomerular capillary mean pressure is 54 per cent of the aortic pressure. The average aortic pressure was found to be 37 cm. of water, so glomerular capillary pressure is about 20 cm. The colloid osmotic pressure of frog's plasma, which is the pressure which must be exceeded before a protein-free fluid can be separated by filtration through the glomerular membrane, is less than 10 cm. These figures demonstrate that the blood pressure in the glomerular capillaries is ample to produce a filtrate.

These analyses, the figures for capillary pressure, together with the results of numerous experiments on the surviving frog's kidney which show correlation between urine rate and height of aortic pressure lead me to think that for these amphibia we have no choice but to decide that the glomerular urine is an ultrafiltrate and that the process by which it is formed is the purely physical process of filtration.

Direct measurements of the volume of filtrate formed in the sum total of the glomeruli of a frog's kidney have not been made. A single glomerulus, however, will often yield 1 cu. mm. per hour, occasionally as much as 4 or more cu. mm. per hour. If these figures are multiplied by the average number of glomeruli which the two kidneys of frogs such as we have used contain (4,000), we get an hourly volume of

glomerular filtrate of from 4 to 16 cc. The rate of urine excretion in normal frogs immersed in water is much less than this: of frogs subjected to the procedures necessary for collection of glomerular urine very much less. Indirect determinations indicate that in frogs the volume of the glomerular filtrate may be as much as 15 or 20 times that of the urine which is elaborated from it. I think we need not hesitate to conclude that excreted urine in amphibia is less in volume than the filtrate from which it is elaborated.

I wish now to question whether there is evidence upon which to base a conviction that the conclusion drawn from the amphibian experiments that the glomerulus is a filter can safely be carried over to the mammalian or human kidney. But before doing so it will be of advantage to discuss one aspect of the physiology of the renal tubule, viz: secretion.

You will recall that Bowman regarded the tubule cells as secretory because of their appearance: Heidenhain, because of their capacity to accumulate indigo carmine within their lumina under circumstances which he believed abolished glomerular function entirely. Other evidence could be outlined, none however as convincing as that provided by the work of E. K. Marshall and his colleagues in Baltimore.

Marshall was aware of the fact that there are fishes whose kidneys consist only of tubules, no true glomeruli being present. *Lophius piscatorius*, the goose fish, and *Opsanus tau*, the toad fish, are those which he studied. These kidneys secrete urine at slow rates which contains urea, creatine and other nitrogenous substances, magnesium, sulphates, highly variable amounts of chloride and phosphate. When creatinine or phenol red are injected these appear in the urine in high concentration. Glucose, injected even in large amounts, is not excreted nor do the fishes become glycosuric when injected with phlorhizin. The chief blood supply of these kidneys is venous and the pressure of urine in the obstructed ureter may rise higher than the blood pressure. In these animals there can be no doubt that the tubule cells are secretory structures.

In work on dogs, Marshall showed with comparable certainty that the rate of excretion of small doses of phenol red, subcutaneously injected, is far too great to be explained by glomerular filtration; that the tubules must play a major part in the transfer of this substance from blood to urine.

For example, in one dog, the amount of phenol red excreted in one

minute was equivalent to that contained in 148 cc. of plasma. Only one-fourth of the phenol red in the plasma was filtrable, three-fourths being combined with the plasma proteins. Hence, to account for the observed rate of phenol red excretion by filtration alone, a filtrate in volume equivalent to *all* of the plasma water from nearly 1200 cc. of the blood would be required. It is clearly impossible that all of the water can be filtered out of the plasma in its passage through the kidney; equally impossible to conceive that enough blood flows through the kidneys per minute to yield 1200 cc. of filtrate. Hence the inescapable conclusion that the tubules participate in the excretion of this dye. As a result of these experiments it is now possible to say with complete conviction that when small doses of phenol red are given to dogs, from 90 to 95 per cent of the dye is excreted by the tubules; only 5 to 10 per cent through the glomeruli.

Professor Homer Smith has shown that a similar statement can be made concerning man, and experiments made in my laboratory indicate that this general conclusion is applicable also to the excretion of indigo carmine in rabbits and of the organic iodine compound known as Hippuran in dogs.

Now to revert to the question whether the evidence permits us to believe that the glomerular process in mammals and in man is one of filtration.

(1) Microscopic study of the glomerulus in the human kidney shows no evidence of the existence of other structures or of more complex cell structures than are to be found in the frog's glomerulus. The epithelium which invests the capillary loops of the glomerulus in man is distinctly less conspicuous than in amphibia. There is no histological evidence of the development of structures which conceivably might serve a more selective process.

(2) The older experiments of Ludwig showed that the mammalian kidney resembles a filter in its response to changes in arterial blood pressure; within limits, urine rate increases and decreases with increase or decrease of blood pressure in the renal artery. The inference that this fact pointed to filtration as a factor in urine formation was contested by Heidenhain in the belief that the simultaneous alterations in blood flow were the variations which caused the urinary changes. This contention has been answered by experiments with rabbits in which artificial arrangements were established which permitted blood pressure

in the renal circulation to be altered independently of changes in blood flow. They showed that when the volume of blood flowing through the renal vessels was kept constant, the rise of pressure in the renal circulation which was produced by nerve stimulation, by the effect of a small amount of adrenalin or by moderate obstruction of venous outflow from the kidney was paralleled in striking fashion by concurrent changes in rate of urine output.

(3) Heidenhain's claim that the diffusible dye, indigo carmine, is not excreted by rabbits through the glomerulus, a claim recently upheld by Professor Bensley of Chicago, is, I believe, based on inadequate experiment. This dye, like phenol red, is to a large extent bound by the plasma proteins, hence a large fraction in the plasma is not filtrable. The curve of its concentration in plasma after an intravenous injection falls very rapidly, so that if one allows a half-hour to elapse between intravenous injection of even a large dose and excision of the kidney for histological examination the concentration of filtrable dye in the plasma may be so low that a filtrate in the capsules at the time of excision gives no color to them which is distinguishable in fixed sections. Furthermore, when experiments are designed in which these two sources of possible error are avoided, clear evidence is obtained that indigo carmine is excretable through the glomerulus in rabbits, its membrane having no selective power to retard its passage.

(4) Finally, study of the renal excretion of the polysaccharide inulin gives evidence which is more than suggestive that mammalian glomerular process is solely one of filtration.

In frogs it was shown that with respect to every one of a considerable number of substances tested the glomerular urine gives evidence of being a filtrate. Among these was the polysaccharide inulin which despite its high molecular weight (5100) and low diffusibility passes through the membrane as rapidly as does the water in which it is dissolved or as do the far smaller molecules of urea, glucose, etc. This necessitates the inference, already stated, that the glomerular fluid is forced out of the blood through openings large enough to interpose no hindrance to these large molecules. In addition it appears that the majority at least may be even larger than this: for when crystalline egg albumin (molecular weight 40,000-44,000) is introduced into the renal circulation of frogs it appears in large quantities in the urine, and is detectable in the glomerular fluid in concentration which seems to be

somewhat less than that of the perfusion fluid. But when crystallized horse serum albumin (molecular weight 68,000) is similarly tested none appears in urine or in the glomerular fluid. These statements give a rough definition of the frog's glomerular membrane, regarded as a sieve. If analogous results can be obtained in mammals, we can be permitted to think of the mammalian membrane in the same terms.

Now when inulin with a molecular weight of 5100 and a diffusion coefficient equal to that of a spherical molecule three times as large, is injected intravenously into dogs, it is excreted with great rapidity and often in very high concentration. For example, in one experiment 70 per cent of an injected dose of 14.5 gm. was excreted in 45 minutes. When egg albumin (molecular weight 40,000) is injected into dogs along with an equal amount of inulin its excretion is slower than that of inulin, though eventually quite as complete. When horse serum albumin (molecular weight 68,000) is injected, scarcely detectable traces of this protein appear in the urine. From this it would appear that the mesh of the glomerular membrane in dogs is approximately the same as in frogs, provided, however, that we can be sure that none of these large molecules are secreted into the urine through the tubule. So far as the egg albumin is concerned, I know of no evidence that it is excreted through the agency of tubule cells; much, chiefly histological, that it escapes through the glomerulus. Concerning inulin, there is a good deal of evidence that none is excreted by tubules, all by the glomeruli. In part, it is this:

(1) The aglomerular kidney of the toad fish is wholly unable to excrete it, even when injected intravenously in large doses.

(2) The frog's kidney is unable to excrete it when it is presented to the tubules only via the renal portal vein.

(3) In dogs and rabbits, whose blood pressure is lowered to a level at which glomerular filtration is impossible, i.e., to that equivalent to the colloid osmotic pressure of plasma, injected inulin does not find its way into the lumina of tubules, whereas simultaneously injected phenol red, or indigo carmine, or Hippuran does.

(4) The rate of excretion of inulin in relation to its concentration in plasma, i.e., its plasma clearance, in dogs and rabbits, is identical with that of creatinine. In animals made diabetic with phlorhizin its clearance is identical with that of glucose (Shannon). It seems incredible that a tubular process of secretion, which we must regard as selective,

should deal in identical fashion with three substances so widely different physically and chemically as inulin, creatinine and glucose; whereas the physical process of filtration must inevitably deal with them alike, provided only that the filter is permeable to all alike, as, in frogs, we have found that it is.

For these several reasons then we may regard the mammalian and the human glomeruli as filters with nearly as sure conviction as that which we hold concerning the amphibian glomerulus.

If the facts and conclusions which have been outlined, particularly concerning the excretion of inulin, are true, viz: that its sole pathway of renal excretion is the glomerulus and its concentration in the glomerular urine is the same as that in the water of the blood plasma, then we have acquired a trustworthy method for measuring the rate at which the glomerular filtrate is formed and delivered into the proximal ends of the uriniferous tubules.

The amount of inulin excreted in the urine in a minute divided by the amount contained in 1 cc. of plasma (i.e., plasma filtrate) gives the volume of filtrate in cc. per minute.

Many such determinations have now been made, most of them in the laboratory of Professor Homer Smith at the New York University Medical College and they show that for adult man under basal conditions 120 cc. per minute is the average rate at which glomerular urine is formed. This value is obtained whether urine is being excreted at the rate of 0.5 cc. per minute as a result of water deprivation or 15 cc. per minute because of excessive water intake, or at intermediate rates.

We have arrived at last at a conclusion substantiated by a large volume of evidence and at variance with none of which I am aware, which seems to me to be of paramount importance in any consideration of kidney function: viz: the beginning of urine formation consists in the separation from blood of a torrent of undifferentiated filtrate by a blind physical force. Its volume is so great as to contain all of the normal constituents of plasma which must be excreted, with the probable exception, for man, of a fraction of the creatinine; it contains also relatively vast quantities of glucose, amino acids and salts which must not be excreted. In the cells of the tubules reside the capacities of restoring to the blood by finely adjusted selective processes of reabsorption those substances which the body must keep. In tubule cells also reside secretory capacities which are responsible for the excretion of

a fraction of injected or ingested creatinine (in man) and of most or much of some foreign substances, of which phenol red may be taken as typical. In the present state of our knowledge we are not required to believe that any of the urea, uric acid, anions or fixed bases are normally secreted into the urine by the tubule cells.

When we find ourselves forced to believe that for the formation of 1 cc. of urine per minute more than 100 cc. of fluid are separated from the blood; that in this separated fluid are contained in 24 hours nearly half a pound of glucose, of bicarbonate, and two pounds of salt, little, if any, of which escape into the urine, we are compelled to realize that reabsorption is the chief task which the tubule is normally required to perform.

Direct evidence of the existence of reabsorptive processes and of the localizations of some has been obtained in the study of the amphibian kidney.

The same methods which were successful in providing fluid from glomerular capsules in frogs and Necturi have also yielded supplies of fluid drawn from different levels of the tubules of these animals. The experiments were far more difficult, however, because of the tortuosity of the tubules and the fact that each is intertwined with its neighbors; because of the narrowness of the lumen, and the necessity of avoiding collection of fluid which had flowed past the point of the collecting pipette; because of the necessity also of accurate identification of the site of puncture with reference to the nephron as a whole. A single nephron was identified by injecting dye into Bowman's capsule and watching its passage through the tubule: the deposition of a globule of mercury or oil in the lumen at a point immediately distal to the point of the pipette prevented reflux; a camera lucida scale drawing of the punctured tubule was made by filling its entire lumen with india ink, fixing the kidney and clearing the part containing it. The puncture hole was easily visible in the cleared preparation and measurements of the distances to the ends of the segment of tubule in which it occurred were accurately made. Obviously the analytical methods developed in connection with the glomerular problem were equally applicable to fluid from the tubule.

Before stating results it should be emphasized again that the urine of amphibians is always, normally, more dilute than the glomerular filtrate. This is largely due to absence of chloride and bicarbonate from

the urine. It doesn't necessarily mean, however, that the processes of urine formation in amphibia are unlike those in mammals. Frog's urine always contains urea in higher concentration than blood—under conditions of dehydration as much as 70 times that of blood. The balance between processes of reabsorption and those of concentration is different in two orders; there is no reason for thinking that the nature of the processes is different.

One group of results shows that the glomerular filtrate passes through the entire length of proximal convoluted tubule with little change, either in the total concentration of dissolved substances or in the concentration of chloride. It is only during passage through the lumen of the distal convoluted tubule that the total concentration and the concentration of chloride diminish. From these analyses it is possible to assert that the selective, active reabsorption of NaCl in amphibia is a definite function of the distal and not of the proximal convoluted tubule.

In striking contrast with the behavior of chloride is that of glucose. As soon as the glomerular filtrate has progressed an appreciable distance along the proximal tubule, its glucose content is significantly diminished. When half way through, the reabsorption appears to be complete or nearly so. Special experiments in which glucose solutions were perfused through the distal half of the proximal tubule and also through all of the distal tubule showed that the capacity of reabsorbing glucose is possessed by all of the cells of the proximal tubule but not by any of the cells of the distal tubule (Drs. Walker and Hudson).

The reaction of the fluid in the tubule remains essentially the same as that of blood plasma during its progress through the entire proximal tubule (Drs. Montgomery and Pierce). At a certain point in the distal tubule it begins to become acid. By injecting indicator solutions (phenol red) into the distal tubule, Dr. Montgomery found that the cells which are responsible for the acidification of urine are localized in a region corresponding roughly to the middle third of the distal tubule. There are the best of reasons for believing that reabsorption of base from the tubular fluid is responsible for its acidification.

Visual evidence was long ago obtained of reabsorption both of base and of water. The lumen of a single tubule was distended with a dilute solution of phenol red by intracapsular injection. The tubule was blocked by pressure with a glass rod so that no more fluid could enter the tubule; that within it remained stationary. The colored streak which revealed the

lumen gradually changed from a broad, lightly colored band to a narrow thread of concentrated color. Fluid was leaving the lumen, the dye was retained within it. The color remained red until the blocking rod was lifted. Then the column of fluid moved on down the tubule and its color changed abruptly to the yellow tint, which represents acidity, at the level in the distal tubule at which, we must believe, base is reabsorbed.

These reabsorptive processes are abolished when the tubule cells are poisoned as by HCN or $HgCl_2$. They are not to be explained by diffusion or, so far as I am aware, by any other familiar physical process. They continue to operate when the fluids within and without the tubule are of identical composition, i.e., when no initial diffusion gradients exist.

The time which was allotted to me is past. Evidence has been outlined which seems not only to justify but to necessitate belief that the first function of the kidney is to separate a filtrate from blood in volume so enormous as to contain all of the waste products of metabolism and the unneeded salts and water. Necessary as this function is, were it uncorrected, death from dehydration and loss of bases would inevitably and promptly ensue.

Corrective processes of reabsorption by which escape of water, salts and diffusible nutrients essential for survival is prevented are distributed among the different segments of the tubules. These are the processes which are finely adjusted to serve the varying excretory requirements of the body as a whole. By chemical rather than by nervous messages, tubule cells are informed of small changes in the composition of the blood; by mechanisms, as yet beyond description, their response is so discriminatingly effective that the narrow optimal range of its variations is preserved.

Tubule cells also excrete. The demonstration of this capacity in the mammalian kidney is as yet limited largely to the excretion of substances which are not normal products of metabolism or constituents of the normal diet. Its mechanism is wholly obscure. It may be that future work will show that this capacity is more important in normal urine formation than present knowledge indicates. If so revisions of current belief will be necessary.

The information upon which these statements are based is significant in that from it we gain clearer definition of future problems and more secure foundations of interpretations.

THE NATURE OF THE VISUAL PROCESS

Harvey Lecture, October 21, 1937

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I. HISTORICAL ORIENTATION

THIRTY YEARS ago, about the time the Harvey Society was founded, physiologists were rapidly losing interest in the study of vision and photoreception. During the fifty years preceding that time, physiology had been turbulent with the quarrel between Hering and Helmholtz and their followers. This vigorous and frequently acrimonious debate had served its purpose of stimulating research and clarifying the ideas involved. But with the death of Helmholtz and Hering, the argument as well as the patience of physiologists wore itself out; and by 1915 even the efforts of Ladd-Franklin to revive it in this country aroused only an amused or bored tolerance on the part of physiologists. The quarrel seemed far from the center of physiology, and our imagination and interest could not be fired by the problems. It is no wonder then that during the existence of the Harvey Society no one before today has lectured to it on the physiology of vision. Before progress could again be made in this field, there had to be a period of quiescence out of which was to come a new orientation.

The historical quarrel had been about the facts of color vision and about its theoretical basis. The new impulse, which twenty years ago began to revivify the study of vision, came from an entirely new quarter. Physiology as a whole was just beginning to feel the powerful influence of the rapidly growing science of physical chemistry; and the moribund subject of vision shared in the general stimulation which resulted.

Its special activating agent was that portion of physical chemistry known as photochemistry. This was a new science, which had just grown up from its early beginnings by Grotthus, Draper, Bunsen, and Roscoe, through its adolescent period by Luther and Weigert, and had only just received its coming of age recognition in the form of

Einstein's Photochemical Equivalence Law. In 1911 Weigert had summed up its available knowledge in a thin volume in German, and Sheppard in 1914 had organized the field in English in a more bulky monograph. Here then was knowledge which could be drawn on for an understanding of the nature of vision and photoreception.

New impulses are never completely new; and what at first appears as a break with traditionally accepted views, often turns out to be really in the tradition, the connection having become obscured in the period preceding the break. About a hundred years ago, when Niépce and Daguerre discovered how to fix an image produced photochemically, Moser (1842) had suggested that the action of light on the retina was similar to the action of light on photosensitive materials generally. Such a photochemical idea of retinal action was accepted by many physiologists. It received dramatic confirmation by Boll's discovery in 1876 of a light sensitive substance in the retina and by Kühne's extraction of this substance, visual purple, a year later.

Kühne's (1879) beautiful researches with visual purple raised hopes for a speedy solution of the problems of vision. But these hopes were quickly disappointed, and that for two reasons. In the first place, neither visual purple nor any similarly sensitive material could be extracted from the cones; and the cones are the elements which mediate color vision and most other visual functions under ordinary conditions. In the second place, the behavior of visual purple did not seem easily to be related to the specific properties of vision as they were then known. Therefore, in the excitement of the color vision debate, visual purple and photochemical notions were relegated to the background.

The new interest in photochemistry brought these ideas back, but it was not visual purple which led to the photochemical study of vision, but precisely the reverse. It was the developments in photochemistry which were first applied to the solution of visual problems, and these later brought a renewed interest in visual purple.

Perhaps the first efforts to apply concrete photochemical ideas to vision and photoreception were made by Lasareff in 1913, and independently a little later by Pütter (1918) and by myself (Hecht, 1918). With these as beginnings, a new interest has developed and has grown into an increasingly larger volume of researches and ideas, ripe for evaluation and synthesis. My virtue as speaker this evening is merely that the other two pioneers have left the field, while I have persisted.

II. Point of View

Before presenting some of these researches, it is well to formulate the point of view which underlies them, since it must form the background of the story. A process, such as vision in man, represents a complicated series of events. It is not only the photoreceptor process itself which takes place in the outer end organs; but the nerve impulses which come from them, and which, when joined by other impulses, then pass through the various pathways to be transmitted, amplified, and perhaps altered, until the final results at the cortex are achieved. Nor is the photosensory system of other animals much simpler. The receptor system is there, impulses are involved, ganglia have to be passed, and reflexes have to be initiated.

Since all these elements enter into the end result, they surely influence its characteristics to some extent. The question is to what extent? And the answer can be secured only by experiment. Our own idea has been that no matter what enters in the chain of events, the ultimate place of origin of the impulses which pass along the optic tracts is in the initial action of light on the receptor cells in the sense organ. Therefore, for a number of years we have measured the different functions of vision and photoreception in man and other animals to ascertain how their quantitative properties depend on the characteristics of these very first reactions which must take place between light and the sensitive elements.

Such a viewpoint has become justified by experience. In addition, there are physiological considerations which render it not only acceptable, but compelling. For example, Adrian (1928) has studied the behavior of preparations which are combinations of sense organ and nerve, and he found in all cases that the nerve is far more rapidly acting and far less fatigable than the sense organ. Therefore, what the combination of the two transmits is determined by the events in the sense organ and not in the nerve.

The human eye is a complicated sense organ, and it might seem that the information gained about it would be both complicated and special, and would contribute little toward a basic understanding of the nature of the photoreceptor process. For my own part, I accepted this idea at the beginning and began work with more lowly animals such as the ascidian and the clam. However, as the work progressed, it became apparent that the human eye is just as capable of yielding fundamental

information, provided one has the wit to recognize it. To find the general implications of human vision, it is only necessary to ascertain and to evaluate those of its properties which are special. Once understood, these special conditions may be eliminated experimentally, or measured and corrected for. In the last few years there has therefore accumulated a considerable amount of new and precise data recording the quantitative properties of various visual functions. In addition, many of the older measurements have been freshly examined, and the whole field has achieved a form and unity which it did not have a generation ago. It is my purpose to present only one facet of this pattern for your examination in detail, and to sketch in the rest of it in outline only.

The function to be considered in detail deals with the recognition of flicker. The reason for its choice is first, that it illustrates the essentials of the process as a whole, and second, that its investigation and understanding has in large measure occurred in our own laboratory.

III. Rods and Cones

Two things have to be made clear before it can be considered that we have begun to understand the visual process in the retina. One is the relation of the measurements of visual function to those morphological elements in the retina which are concerned with receiving the light, and the other is the more intimate chemical relation between the absorbed light and the photosensitive substances within the retinal elements. We shall consider the morphological basis before presenting the measurements, and deal with the chemical basis afterwards.

The retinal elements concerned with vision are the rods and cones, whose relative distribution and separate function make it necessary to treat the vertebrate eye not as a single sense organ, but as a double one. This is the duplicity theory which was first proposed by Max Schultze in 1866. It was completely ignored for a generation, and gained recognition only when it was independently developed by Parinaud in 1881 and by von Kries at about the same time. In its essentials the duplicity idea supposes that the retinal cones are the receptors for color vision and for vision at high intensities, while the rods are the general receptors for light regardless of color, and function best at low intensities.

In the human eye, the center of the retina is occupied exclusively by cones, while the rest of the retina contains rods and cones, with rods increasingly predominant toward the periphery. There is a central area

whose diameter is very nearly 1.5° which is completely rod-free, while a slightly larger area, 2° in diameter, contains so few rods that it may be considered practically rod-free (Schultze, 1866; Rochon-Duvigneaud, 1907; Wolfrum, quoted by Dieter, 1924; Østerberg, 1935). As a result, vision at high illuminations is color vision and is most efficiently carried on with the center of the retina, while at low illuminations vision is colorless and is most effective in the periphery.

The necessity for understanding this morphologically and functionally dual nature of the human eye is aptly illustrated in the history and data of flicker. The reason is that this field of knowledge has had a particularly rapid development in the last few years, and the steps in its organization and understanding are easily available.

IV. The Problem of Flicker

When the light from an object is regularly interrupted, the resulting appearance of flicker depends for its magnitude on the frequency of the interruptions. When the frequency is low, the contrast between light and dark is great; but as the frequency is increased, the contrast becomes less, and the flicker can disappear completely when the frequency of interruptions is made sufficiently high. The precise point at which flicker disappears is known as the critical fusion frequency, and may be determined with considerable accuracy. As a result, its value has been shown to depend on a variety of conditions.

The most basic factor which controls the critical frequency is the intensity. Though the dependence of the critical frequency on illumination was recognized over one hundred years ago by Plateau (1829) and is evident from the work of Emsmann (1854) and of Nichols (1884), it was only forty-five years ago that Ferry (1892) formulated what has since become known as the Ferry-Porter Law, namely, that the critical frequency is proportional to the logarithm of the illumination intensity. Ferry's published measurements support this formulation only in the most general way, but the later data of Porter (1902) are adequate for its statement. Porter's work was corroborated by Kennelly and Whiting (1907), by Ives (1912), and by Luckiesh (1914).

Porter's measurements did more than establish the validity of the logarithmic relation. They pointed distinctly toward the separate function of the rods and cones in flicker. When his data of critical fusion frequency—as cycles of light and dark per second—are plotted against

the logarithm of the intensity, they fall on *two* straight lines instead of one. The slope of the line at low intensities is 1.56, while that of the line at high intensities is 12.4, and their interpretation as rod function and cone function respectively is obvious in terms of the duplicity theory. Porter's findings were confirmed by Ives (1912), whose data for different parts of the spectrum also show a dual logarithmic relation. However, the slope of the straight lines and their point of intersection seem to vary with the wave-length of the light, the upper and lower limbs of the relationship varying in different ways. In addition, Ives found the extraordinary fact that for blue light the low intensity line becomes horizontal.

These peculiarities were difficult to reconcile with the simple duplicity interpretation, and this difficulty was emphasized by Allen (1919, 1926) who drew through his measurements about five short straight lines of different slope instead of the usual two. The data presented by Allen do not justify this treatment; the points appear to lie on a continuously curving line, but their continuity is obscured by Allen's neglect of such experimental precautions as fixation, the presence of an adequate surround, and the proper adaptation to each intensity. The work of Lythgoe and Tansley (1929), which took all these precautions, distinctly gives no support to Allen's multiplicity of straight lines.

Lythgoe and Tansley's measurements confirm the logarithmic relation of intensity to fusion frequency, but Lythgoe and Tansley attach no importance to its strict formulation as done by Ferry, by Porter, and by Ives, and consider that their data agree only under certain conditions with the linear relation of critical frequency to log *I*. The same may be said about the measurements of Granit and Harper (1930), who found that for a range of about 1 to 1000 in intensity, the critical frequency is very nearly directly proportional to the logarithm of the intensity. For higher intensities the relationship does not hold, and the curve of frequency against log *I* tends to become horizontal, as already found by Grünbaum (1898).

One striking thing appeared in the work of Lythgoe and Tansley. Ives had found that for blue light the lower limb of his data is horizontal, and in this he had been confirmed by Allen. Ives thought that this was a special property of blue light. However, Lythgoe and Tansley recorded that when measurements are made with a retinal area 10° off-center, the lower portion of the data tends to be horizontal even for white light, and they correctly interpreted this horizontal portion as

due to the appearance of rod function in the periphery at low intensities.

The confusion in flicker measurements which caused Lythgoe and Tansley to explore the influence of fixation, surround, and adaptation on critical frequency, also prompted us independently to study flicker; this, and the fact that none of the measurements existing at the time, nor those published during our investigations, covered a range of intensities sufficient to define the relation between critical frequency and intensity over the functional range of the eye. Since then, we have measured this relation for different portions of the retina, for different sizes of field and for different colors, for as large a range of illuminations as possible, and under such conditions of fixation and surrounding illumination as to render the data reproducible and definitive. As a result the confusion has disappeared, and the conflicting data have become understandable and consistent with other visual knowledge.

V. Central and Peripheral Measurements

If the separation of rod and cone function first suggested by Porter's data is correct, it should be possible to isolate these two functions by using the known structure of the retina. The central 2° of the retina is practically rod-free. Therefore, the relation between fusion frequency and intensity, if measured with central areas smaller than 2° in diameter, should be a continuous function representing cones, whereas with larger areas or with similar small areas outside the fovea, the relation should show a duplex character illustrative of the predominant working of rods at low intensities, and of cones at high intensities.

The measurements of Hecht and Verrijp (1933*b*) with a small field located centrally and peripherally show this expectation to be correct. Fig. 1 shows two sets of measurements made several years apart (Hecht and Verrijp, 1933*b*; Hecht and Smith, 1936) with a 2° field situated in the fovea. The data demonstrate that for the rod-free fovea there is one continuous relation between critical frequency and the logarithm of the intensity. The relationship is distinctly sigmoid, the S-shape being rather drawn out. In the middle range of intensities, the data lie with reasonable precision on a straight line and thus confirm Porter, Ives, and the other workers, even to the extent of having a slope of the same magnitude as found by them.

Below the middle range the data form a gentle curve which stops fairly abruptly when with central fixation the field appears uniform

even when the test area is extinguished. At the highest intensities the relation between critical frequency and log *I* rapidly ceases to be linear. The curve flattens out, and, as with other visual functions such as intensity discrimination and visual acuity, remains flat provided the adaptation and surround are adequate.

Using the same sized field (2° in diameter with a non-flickering 10° surround) we measured the relation between critical frequency and intensity at 5°, 15°, and 20° from the center. The results are shown in Fig. 2, and are strikingly different from the central data in that they clearly fall into two parts. The first is at low intensities, where the critical frequency first rises with log *I* and then reaches a maximum which is maintained approximately constant for about 1.5 logarithmic units. The total intensity range covered by this rise and plateau is about 3.5 logarithmic units. The second part also begins with a rise in critical frequency as log *I* increases, and also terminates when the critical frequency reaches a maximum. The intensity range covered by the second part is about 4 logarithmic units. The same results obtain in whatever peripheral direction of the eye the measurements are made.

Since the central 2° field falls within the relatively rod-free area of the retina, the continuous nature of the data mark them as a function of the cones alone. The double nature of the peripheral measurements very likely represents rod function for the low intensity section, and cone function for the high intensity section. This is borne out by the increas-

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Fig. 1. Critical frequency and illumination. The data show a comparison for the same eye (S. H.) using central fixation and a 2° flickering field, between measurements made several years apart with a 10° surround (Hecht and Verrijp, 1933*b*) and with a 30° surround (Hecht and Smith, 1936).

Fig. 2. Relation between critical frequency and log *I* for white light with a 2° field in four retinal locations: at the fovea, and at 5°, 15°, and 20° above the fovea. The data are from Hecht and Verrijp (1933*b*). Due to an error in the original paper, the intensities have had to be multiplied by 40 to convert them correctly into those here given.

Fig. 3. Influence of the area of test field on the relation between critical frequency and log *I* (Hecht and Smith, 1936).

Fig. 4. Area and the flicker relation. The log *I* axis is the same for all the data. The numbers on the log frequency axis to the left apply to the uppermost data only; the other data have been moved down in steps of 0.2 log unit in order to space them, and their precise position is given on the right. The curves are from equation (3) to be derived later, in which for the cone portions $m = 2$, $n = 2$; and for the rod portions $m = 2$, $n = 1$. *Cf.* Fig. 13 shown later.

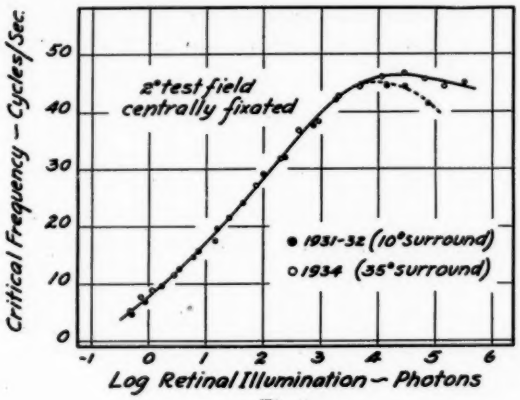
Critical Frequency – Cycles/Sec.
2° test field centrally fixated
● 1931-32 (10° surround)
○ 1934 (35° surround)
Log Retinal Illumination – Photons

Fig. 1

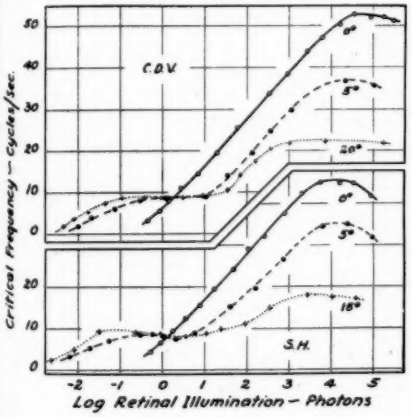

Fig. 2

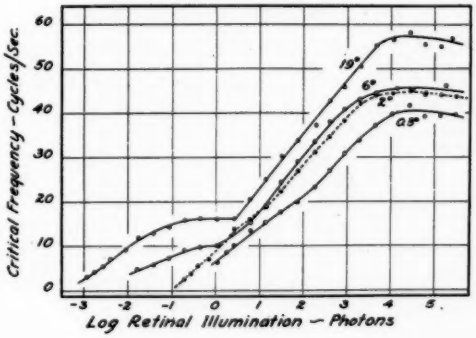

Fig. 3

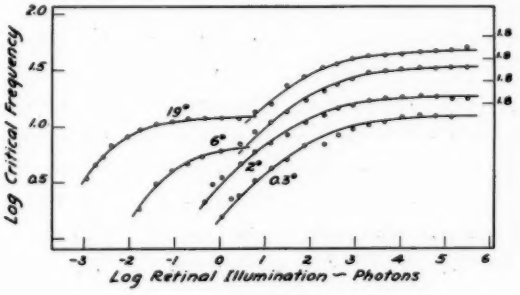

Fig. 4

ing separation of the two sections as measurements are made farther and farther from the center: the cone section shifts to higher intensities and the rod section to lower intensities, as would be expected from the increasing ratio of rods to cones in these regions.

VI. Area and Flicker

We have also measured the relation between critical fusion frequency and intensity for four centrally located areas 0.3°, 2°, 6°, and 19° in diameter, and our measurements (Hecht and Smith, 1936) confirm these conclusions. The data for E. L. S. are in Fig. 3, and, as expected, those for 6° and 19° break sharply into two sections while the 2° and 0.3° fields show only one continuous function. The slight bend in the latter data need not concern us here; it is certain that the bend is not due to a slight admixture of rods.

Fig. 4 presents the data of S. H. plotted as the logarithm of the critical frequency against the logarithm of the intensity. This type of plot shows more strikingly the phenomena already described. In spite of the irregularity in the 0.3° data, a single curve describes the measurements fairly well. The same single curve is even more expressive of the 2° data, and it is also drawn through the cone portions of the 19° and 6° data.

The rod sections of 19° and 6° require a slightly different curve which is the same for the two fields. It is worth emphasizing that the rod sections of the two large fields have the same curve drawn through them. While this is not clearly seen in an ordinary graph of critical fusion frequency against log I, it becomes plain in the log-log plot of Fig. 4. This is because on a log-log plot of this kind the shape of the curve relating critical frequency and intensity is invariant, and uninfluenced either by the intensity units or by the absolute values of the critical frequency, since these merely shift the position of the curve on the two axes. The identity of the curves for 19° and 6° shows that the difference between them is not basic, but merely represents a change in one of the constants in the equation which describes them.

Exactly the same is true for any systematic differences which the cone data show. Fundamentally the systems in the rods and cones which determine the relation between critical frequency and intensity remain the same regardless of area. Only the parameters are altered by changing the area. This has finally been recognized by those investi-

gators who are interested in studying the influence of various factors on visual functions. For example, Smith (1936), who was concerned with synaptic and other nervous influences on intensity discrimination, has found that the basic intensity discrimination relation remains unaltered, and that the best way to describe these various nervous influences is to record their effects on the parameters of the fundamental equations (Hecht, 1935) for intensity discrimination. The same thing should be possible with flicker.

VII. Spectral Measurements

In order to confirm the identification of the two sections shown by the measurements which include the periphery, we have studied the relation of critical frequency to intensity in different parts of the spectrum. The reason for such an investigation, and the results to be expected from it, may be understood by an examination of Fig. 5 which shows the sensibilities in the spectrum of the cone system and the rod system. The data record the relative energy at each wave-length required to elicit a minimal visual effect by each system. Each curve is accurate by itself, but the vertical separation between the two is arbitrary. This separation varies with the position on the retina; but with all positions it is true at the red end of the spectrum that there is very little separation between the rod curve and the cone curve, and that the cone curve is always above the rod curve.

Fig. 5 tells us that beginning at the lowest energy level and moving vertically along any ordinate, no visual effect is produced until the rod curve is reached. The resulting sensation will be colorless and will continue to be controlled by the rods as the energy increases until the cone curve is reached, at which point one will begin to recognize color. The significant point of Fig. 5 is that this photochromatic, rod-cone interval varies with the wave-length, being very small in the red, and large in the blue. This is indeed represented by the well known fact that the colorless and color thresholds of the eye are very nearly coincident in the red, but are widely different in the blue (Charpentier, 1880).

The result of all this is that the relation between critical frequency and illumination when measured with red light should show little or no rod section, while with blue and green lights the rod section should be large; for intermediate parts of the spectrum the rod section should

be intermediate in extent. Since preliminary investigation (Hecht and Verrijp, 1933*a*) showed these expectations to be correct, we measured in detail (Hecht and Shlaer, 1936) the relation between intensity and critical frequency for different parts of the spectrum with a circular test field 19° in diameter, surrounded by a non-flickering area 35° in diameter.

The information conveyed by the measurements can best be understood from their graphic representation. As Fig. 6 shows, the data break into two sections. The high intensity portions, identified with cone function, fall together for all the colors. The low intensity sections, identified with rod function, are spread out much as expected, and extend to lower and lower intensities with decreasing wave-length.

Fig. 6 resolves the mystery of Ives' old measurements showing that the low intensity portions of critical frequency data which he found for different parts of the spectrum may be represented by straight lines which differ in slope, the red being steepest and the violet being prac-

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Fig. 5. Relation between wave-length and relative energy required to produce a specific visual effect at high and at low illuminations. The lower data are from Hecht and Williams (1922) and represent the relative energy required to produce a barely perceptible brightness after prolonged dark adaptation. The upper data are from Hyde, Forsythe and Cady (1918) and give the relative energy to produce a given high brightness, using only the fovea. The two curves are each accurately drawn from their separate data. Their vertical separation, however, has been arbitrarily arranged so that they are nearly coincident at the red end of the spectrum; this is a graphic expression of the fact that the colorless and color thresholds of the eye are nearly identical in the red.

Fig. 6. Critical frequency and log I for different parts of the spectrum for the eye of S. H. (Hecht and Shlaer, 1936).

Fig. 7. Critical frequency and intensity for different spectral regions for the eye of S. S. (Hecht and Shlaer, 1936) plotted as log frequency against log intensity. The numbers on the ordinates to the left apply to the topmost data; for convenience, the others have been moved down in steps of 0.2 log unit, and their exact positions are indicated to the right. The curves are from equation (3) to be derived presently, in which for the cone portions $m = n = 2$, and for the rod portions $m = 2$, $n = 1$.

Fig. 8. The relation between critical fusion frequency and intensity for four species of fish. *L* is for the sunfish *Lepomis* (Wolf and Zerrahn-Wolf, 1936); *X* is for the swordtail, *Xiphophorus; P* for the black platy, *Platypoecilius;* and *B* for the Black Helleri which is a complicated cross between the sword tail and the black platy (Crozier, Wolf, and Zerrahn-Wolf, 1937). The ordinates apply to the *Lepomis* data; the other measurements have been lowered 0.5, 1.0, and 1.5 log units respectively merely to keep them apart. The curves through the measurements are from equation (3) with the values of m and n as given for each species.

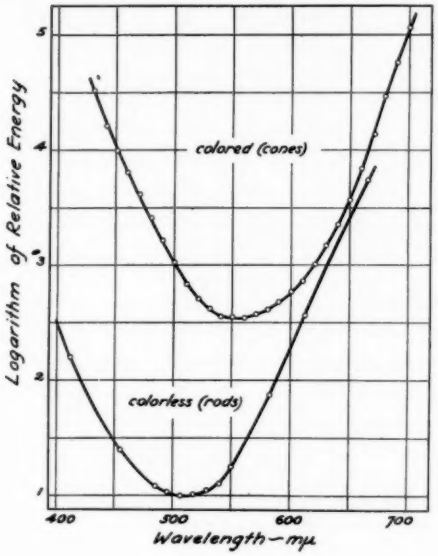

Fig. 5

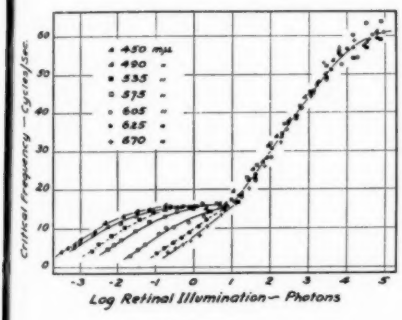

Fig. 6

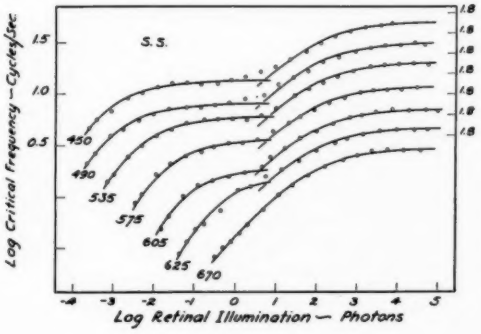

Fig. 7

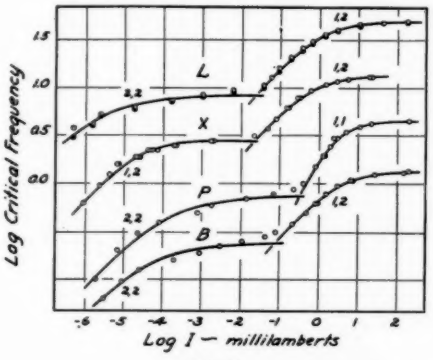

Fig. 8

tically horizontal. It is apparent in Fig. 6 that for short stretches near the rod-cone transition, straight lines can be drawn through the rod data, showing different slopes for the different wave-lengths.

The real phenomenon, however, is something quite different. It is that the separation of rod and cone sections as a whole increases as the wave-length decreases. This is shown strikingly by Fig. 7 in which the data of S. S. are plotted as the logarithm of the critical frequency against the logarithm of the intensity. The data for 670 mμ fall on a single, continuous curve, whereas the data for all other parts of the spectrum are best described by two separate curves. The transition between the two portions is quite sharp for all but the blue and violet data. The high-intensity cone curve is in the same position for all colors, and the only effect of changing the spectral composition of the light is to shift the position of the low-intensity rod curve along the intensity axis, without in the least changing its form.

The identification of rod and cone function is borne out by subjective observation. At low intensities and below the critical fusion frequency the flicker is distinctly located in the peripheral portion of this 19° field so that the field resembles a flickering doughnut, and the last appearance of flicker is always in the periphery. With increasing intensity the first sign of approaching cone function is the appearance of color in the field, which becomes identifiable with certainty about 0.5 log unit below the actual inflection point of the measurements.

At the intensities around the transition, two separate loci of flicker are very often apparent near the critical frequency: one in the periphery, and the other in the center. At intensities higher than the transition intensity but near it, flicker usually persists longest in the center, but beyond these intensities the last trace of flicker may be in any part of the field. Obviously the rods determine the low intensity section and the cones the high intensity section.

VIII. Other Vertebrates

Other vertebrates such as the bony fishes are known to have rods and cones (Schultze, 1866; Wunder, 1925); and Bauer (1910, 1911) and von Frisch (1925) found that they show the Purkinje phenomenon, indicating that their high and low intensity visibility curves differ in position on the spectrum. Using the method of moving stripes which we developed for work with animals other than man, Grundfest (1932)

actually determined the two visibility curves for the sunfish *Lepomis*, and found the low intensity maximum at 540 mμ and the high intensity maximum about 45 mμ farther in the red. It is therefore to be expected that the visual functions of fish should also show a double form representing rod and cone behavior.

This is true. Wolf and Zerrahn-Wolf (1936), using the moving stripe method, have made critical frequency measurements with the same species of sunfish used by Grundfest. Just as Grundfest found two visibility curves, so Wolf and Zerrahn-Wolf find two limbs to the flicker data, indicating separate rod and cone function. As Fig. 8 shows, the intensity separation of the two limbs is more than 4 log units, the main rod section being almost impossible to measure because it lies below the threshold of human vision. Very recently Crozier, Wolf, and Zerrahn-Wolf (1937) have reported flicker measurements with three other species of fish. The data are all given in Fig. 8, from which it is apparent that the separateness of rod and cone behavior in the visual functions of fish is amply established.

IX. Other Visual Functions

Out of the detailed study of flicker there have come two characteristics of the dependence of visual function on intensity. One is the separateness of rod and cone behavior corresponding to expectation from the duplicity theory. The other is the increase in effectiveness of visual function with the increase in intensity to which the eye is adapted. In each system the increase is at first rapid and gradually reaches a maximum which is maintained. Both these characteristics are evident in all other visual functions which have been studied in relation to intensity. I shall illustrate this with visual acuity and intensity discrimination, though it is apparent in other functions as well (*cf.* Hecht, 1937).

Fig. 9 shows Koenig's (1897) measurements of the relation between visual acuity and the intensity to which the eye is adapted. Visual acuity is defined as the reciprocal of the angular distance which must separate two contours in order that they may be recognized as discrete, the unit of separation being a minute of arc. The dichotomy of the data in Fig. 9 is startlingly clear. With red light there is one continuous function which is obviously that of the cones. With white, green, and blue lights there are two relationships,—one at high intensities and

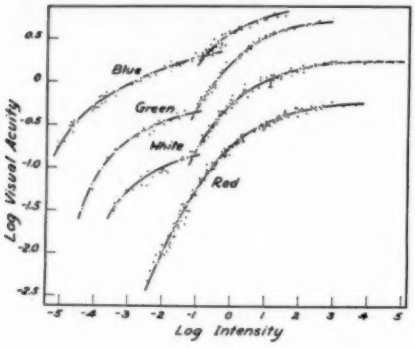

Fig. 9

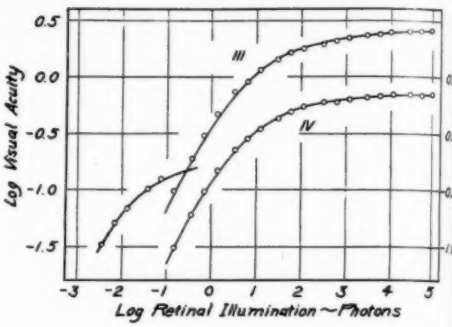

Fig. 10

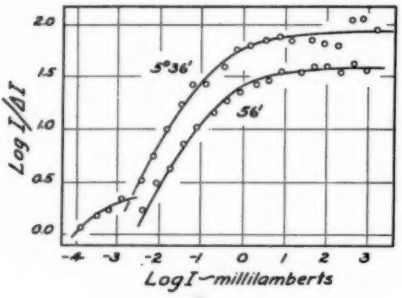

Fig. 11

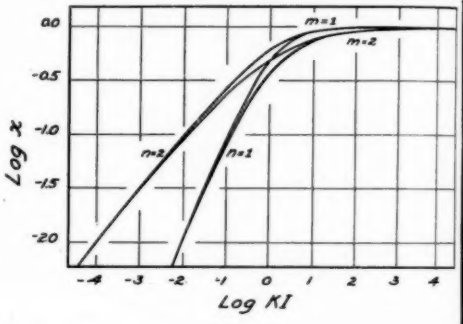

Fig. 13

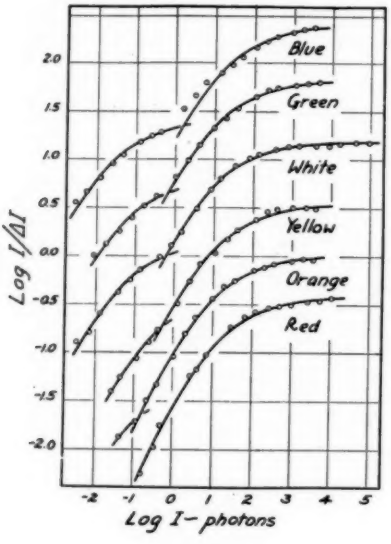

Fig. 12

the other at low intensities. The high intensity limb for all the colors is the same as for red, and thus represents cone function; by the same token, the similarity of the low intensity portion for blue, green, and white, and its complete absence in the red, mark it as the expression of rod function. In particular, note the position on the intensity axis and the relative size of the rod portions for blue, green, and white. The blue section is largest, the green next, the white next, and the red is non-existent, just as we found with flicker.

Shlaer has very recently (1937) made visual acuity measurements with white light in which the function was deliberately confined to the rod-free center of the retina. As was to be expected, he found that under such circumstances the relationship between visual acuity and

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Fig. 9. Visual acuity and illumination for different colors (Koenig, 1897). The intensity axis is the same for all the colors. The numbers on the visual acuity axis apply only to the data for white light. For convenience in showing the data, the red measurements have been displaced downward 0.5 log unit; the green, 0.5 log unit upward; the blue, 1 log unit upward. The separation of the data into two sections needs no emphasis.

Fig. 10 Visual acuity as related to intensity for two observers (Shlaer, 1937). In each case the cone measurements were specifically confined to the fovea. The curves through the data are from equation (3) with $m = n = 2$ for the cones, and $m = 2$, $n = 1$ for the low intensity rod section.

Fig. 11. The relation between intensity discrimination and intensity with different retinal areas and with white light (Steinhardt, 1936). The lower data for an area approximately 1° in diameter show only cone function and are described by equation (3) where $m = n = 2$. The upper data with a much larger area show both rod and cone function. Here too the cone section is described by equation (3) with $m = n = 2$; while the rod data are too few for critical determination, the curve through them has the same values of m and n as the cone section.

Fig. 12. Intensity discrimination at different intensities for different parts of the spectrum. The ordinates are correct for the measurements with white light; those for green and blue have been raised 0.5 and 1.0 log units respectively while those for yellow, orange, and red have been lowered 0.5, 1.0, and 1.5 log units respectively merely to separate the points. For red the data are continuous and represent one functional system only, the cones. For the other colors a second system, the rods, becomes more evident at low intensities as the color moves toward the blue. As usual in visual measurements, white light behaves much as yellow light. The curves are from equation (3) with $m = n = 2$ for the cone section; the rod section is also best described by the same values. The discrepancy near the transition between rods and cones for blue light shows up frequently with blue light measurements of other visual functions; *cf.* Fig. 7 for example.

Fig. 13. The steady state equation (3) plotted when m and n are each 1 and 2. Because of the log plot the shape of the curves remains constant regardless of the values of K and a.

intensity is continuous and single, whereas similar measurements including the periphery show the usual double relationship. His data are shown in Fig. 10.

The increase in visual acuity which the eye shows with rising intensities has been known since Mayer first investigated it in 1754. What Koenig's measurements show in addition is that this increase is true for both rods and cones, and that the rate of increase slows up for each section. Indeed, Shlaer (1937) found that at intensities ten and even a hundred times higher than those attained by Koenig, visual acuity remains constant at a maximum value depending on the test object and on the pupil size.

Intensity discrimination shows precisely the same two properties as do visual acuity and flicker. If I and $I+\Delta I$ are two intensities which can just be recognized by the eye as differing in brightness, then the fraction $I/\Delta I$ is a direct measure of intensity discrimination. When the eye can tell only large differences in brightness, its intensity discrimination is poor and the fraction $I/\Delta I$ is small; whereas when the perceptible difference ΔI is slight, the capacity for intensity discrimination is good, and the fraction $I/\Delta I$ will be large.

Intensity discrimination has been measured by Aubert (1865), by Koenig and Brodhun (1888), by Blanchard (1918), and others. Since I have already reviewed the extensive data on this subject (Hecht, 1935; 1937), it is unnecessary to go into it here; I shall therefore confine myself to two examples, chosen to illustrate the critical points involved. Steinhardt (1936) working in our laboratory was able to show that when intensity discrimination is measured at different intensities with white light, the results depend on the retinal location of the measuring area. With centrally-fixated test areas larger than 2°, his measurements without exception fall on a double curve showing rod and cone function, while for smaller areas they always form single curves like those for flicker and visual acuity under the same circumstances. Fig. 11 shows two examples of his measurements, one with a test field 56′ in diameter, and the other 3° 44′ in diameter. The difference between them, and the meaning of the difference is obvious.

We (Hecht, Peskin, and Patt, 1937) have recently measured the relation between intensity discrimination and intensity for different parts of the spectrum. The results are shown in Fig. 12, and it is unnecessary to comment on them at length. They show essentially what

flicker and visual acuity showed, namely that there are two visual systems which seem to operate separately, and that for each system the visual function becomes better and more effective as the intensity is increased.

It will not have escaped the reader that the way in which visual function and intensity are related is similar for the three properties here presented. This will become more evident when the nature of the receptor process has been discussed and quantitatively formulated.

X. Photochemistry and Vision

In building a picture of the intimate chemical and physical events which underlie the visual process, we may start with the most general ideas about its nature. There are three things which must take place. First, there has to be a sensitive substance which absorbs light and is changed by it into one or more active products. Second, it is necessary to maintain a supply of this photosensitive material; otherwise it would be used up and the process would come to an end. These two processes may be called the primary light and primary dark reactions. Third, the active photoproducts of the primary light reaction must do something of which the end result is an impulse from the receptor cell. This is the secondary dark reaction.

These three requirements are the minimum essentials. The photoreceptor process itself is certainly more elaborate. Moreover, vision involves more than the photoreceptor process alone. Yet it is a fact of pertinent interest that the behavior of many visual functions may be formulated in quantitative detail in terms of these minimum essentials alone. Certainly the three visual functions of flicker recognition, intensity discrimination, and visual acuity may be described in this way.

Let us examine the properties of the simplest photochemical system which can be suggested as corresponding to the primary light and dark reactions. Consider a photosensitive substance S whose total initial concentration is a. Let light of intensity I shine on it, and as a result let there be produced the photoproducts P, A, etc., whose concentrations at the moment t is given by x. The rate at which this primary light reaction $S \rightarrow P+A$ goes will be proportional to the intensity and to the concentration $(a\text{-}x)$ of sensitive material; this may be written

$$dx/dt = k_1 I\ (a\text{-}x)^m \qquad (1)$$

where m is the order of the reaction, and k_1 is a velocity constant which includes the absorption coefficient.

Let us further suppose that some of these photoproducts P, A, etc., can reunite by themselves or with the help of additional substances or energy to form again the sensitive material S. The velocity of this primary dark reaction $S \leftarrow P+A$ will be proportional purely to the concentrations x of the photoproducts; this becomes

$$-dx/dt = k_2 x^n \qquad (2)$$

where n is the order of the reaction and k_2 is its velocity constant.

When such a system of two reactions is steadily exposed to light, corresponding to the adaptation of the eye to a given light intensity, the two reactions proceed simultaneously until their velocities become equal, and the system reaches a stationary state. Putting equations (1) and (2) equal to each other, and rearranging terms, we get

$$KI = x^n/(a-x)^m \qquad (3)$$

where $K = k_1/k_2$. This is the equation of the photostationary state of the simple reversible photochemical system $S \rightleftharpoons P+A$.

Again it is necessary to emphasize that this formulation is too simple to correspond to what the photoreceptor process probably is (*cf.* espepecially, Wald and Clark, 1937). But at the same time it is also important to state that the three visual functions presented in this paper all behave as if they were controlled by just such a simple system as represented by the stationary state equation (3). In fact, so close is the relation between equation and data that it is possible to determine from the measurements the numerical values of m and n.

Equation (3) may be studied by putting a equal to 100 per cent, and computing the values of KI for different values of x after n and m have been given values of 1 or 2. The results of such a series of computations are shown in Fig. 13. Because of the logarithmic plot, the curves keep their shapes regardless of the magnitudes of K or of the units in which a and x are measured. It is the values of m and n which determine the specific shapes and slopes of the curves.

It can be shown that at the stationary state produced by a given intensity I in such a photochemical system, the critical frequency is directly proportional to x, while the intensity discrimination $I/\Delta I$ and the visual acuity are both directly proportional to x^n. It would take us too far afield to reproduce the derivations here, but they are simple and straightforward, and have been presented in detail elsewhere (Hecht, 1935; 1937). Because of this direct dependence of visual function on x, it is easy to compare the data with the curves of equation (3).

Actually the lines drawn through the measurements in Figs. 4 and 7 for human flicker are the stationary state equation in which for the cones $m = 2$ and $n = 2$, while for the rods $m = 2$ and $n = 1$. Moreover, all the curves through the fish flicker data in Fig. 8 are also from equation (3); for each curve the appropriate values of m and n are indicated in the figure.

Exactly the same is true for the intensity discrimination data in Figs. 11 and 12. The curves here are also that of equation (3). For the cone portion $m = n = 2$ as for flicker. For the rod portion it is difficult to be certain, because in most cases the points are too few; but where the points are many m and n both seem to equal 2, and it is this equation which has been drawn through them.

Shlaer's visual acuity measurements in Fig. 10 are also described by equation (3) of the stationary state. The curves in Fig. 10 have $m = n = 2$ for the cones, and $m = 2$ and $n = 1$ for the rods, just as we found for flicker. I have shown (Hecht, 1937) that Koenig's visual acuity data, when properly corrected for pupil area and efficiency, are also fitted by the same equation having the same values of m and n as Shlaer's for both cones and rods.

The conclusion from such numerical comparisons is clear. The quantitative properties of several major visual functions may be described with adequate fidelity in terms of the simplest theoretical assumptions about the photochemical and chemical reactions which must take place in the retinal elements.

XI. Visual Purple

The assumptions just made in the quantitative description of visual functions involve the existence of photosensitive substances in the rods and cones. What is actually known about such substances in the eye? For the cones no photosensitive substance is known, though repeated efforts have been made to extract one. There must be such a substance or several such substances, since the cone visibility curve undoubtedly represents their combined absorption spectrum. Evidently the sensitive materials are present in such high dilutions that their specific absorption in solution is masked by the other materials extracted with them.[1]

[1] Since this was written, Wald (1937) has reported that digitonin extracts of chick retinas show the presence of two photolabile substances, one with an absorption maximum near 510 $m\mu$ and the other with a maximum near 570 $m\mu$. The former is most probably visual purple, while the latter is the heretofore unknown cone photosensitive substance, which he calls iodopsin, but which may be called less formally visual violet. The chick retina is composed overwhelmingly of cones, though some rods are also present. Nevertheless, Wald's extract indicates a higher photometric density of visual purple than of visual violet even in this essentially cone retina.

For the rods, however, we have visual purple, which may be studied in the retina, or in solutions extracted from the retina.

Kühne (1879) could never separate visual purple from the proteins which were in its solutions. His studies on the destruction of visual purple by heat showed this process to have a high temperature coefficient much like that found later for the denaturation of proteins. This made it probable that visual purple itself is a protein, and we have now rendered it even more probable (Hecht, Chase, and Shlaer, 1937) by determining the molecular weight of visual purple. The value turns out to be about 800,000, which puts visual purple at about the same size as thyroglobulin (Heidelberger and Pedersen, 1935).

Visual purple is not a simple protein. Wald (1935*a*, 1935*b*, 1936) has found that on bleaching, visual purple yields a carotenoid, retinene, which slowly changes to vitamin A. This makes reasonable the relation between states of nutrition and vision, which has been known for centuries. Moreover his work has thus identified visual purple as a conjugated protein belonging to the carotenoid proteins, of which many are known as animal pigments, though none other than visual purple are sensitive to light.

Visual purple shows many properties which fit in with visual knowledge. Among these are its absorption spectrum which has its maximum at the same place as the rod visibility curve (Hecht and Williams, 1922). Also, visual purple even in solution can regenerate its color after having been bleached. Kühne (1879) first recorded this sixty years ago, but since then no one was able to repeat his experiments though many investigators tried. Recently we (Hecht, Chase, Shlaer, and Haig, 1936) have found some of the conditions which make regeneration in solution possible, and have been able not only to confirm Kühne completely but to measure the course of the regeneration reaction and to determine the absorption spectrum of the regenerated material. In addition Chase (1937) has found that for visual purple to regenerate in solution, another photosensitive substance present with it must also be bleached. This new photosensitive material is particularly sensitive to blue light and is different from visual purple.

Kühne knew that *in the retina* visual purple may regenerate in two ways: directly from its photoproducts, and from newly supplied materials. Wald has confirmed and extended these findings, and has even shown that they clarify the behavior of rod dark adaptation which,

under certain conditions, shows two different courses (Winsor and Clark, 1936; Hecht, Haig, and Chase, 1937; Wald and Clark, 1937).

Much is expected from this direct photochemical and chemical approach to the study of vision, and it is to be hoped that the next few years will witness the fruition of these efforts.

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MEMBERS ELECTED

DECEMBER 2, 1937

MEMBERS

Mahlon Ashford, 25 Fifth Avenue
George Jarvis Coffin, 140 East 54 Street
Jean Alonzo Curran,
71 Remsen Street, Brooklyn
William Alden Gardner, 70 East 79 Street
Alexander B. Gutman, 711 West 171 Street
Joseph Dominic Kelly, 140 East 54 Street
Robert McClanahan, 60 East 75 Street
James Lowry Miller, 371 Park Avenue
Leslie Emerson Morrissett, 33 East 61 Street
Richard Joseph O'Connell, Jr.
1160 Fifth Avenue
Sidney Sayre Quarrier,
751 Asylum Avenue, Hartford, Conn.
Dickinson W. Richards, Jr.,
180 Ft. Washington Avenue
Samuel Harry Rosen, Montefiore Hospital
Arthur A. Salvin, 1 West 81 Street
John Edward Sullivan,
60 Gramercy Park North
Donald B. Wells,
580 Asylum Street, Hartford, Conn.

ASSOCIATE

Benjamin Malzberg, N. Y. State Dept. of Mental Hygiene, Albany

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

DECEMBER 2—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Election of Academy officers. ¶ The ninety-first anniversary discourse was the first Joseph Collins Lecture and was delivered by Charles R. Stockard, Professor of Anatomy, Cornell University Medical College; on the subject, The Mechanisms Operating the Body as an Integrated Unit.* ¶ Report on election of members.

DECEMBER 16—*The Harvey Society (in affiliation with The New York Academy of Medicine).* Third Lecture, The Functional Significance of the Lymphatic System, Dr. Cecil K. Drinker, Professor of Physiology, School of Public Health, Harvard University.

SECTION MEETINGS

DECEMBER 3—*Surgery.* Reading of the minutes. ¶ Presentation of cases—a] Lymphosarcoma of the jejunum, Frank Glenn; Discussion by William F. MacFee, John Douglas and Sidney Weintraub; b] 1. Hernia of jejunum and ileum through the transverse mesocolon; 2. Megacolon following the development of an aortic aneurysm, Harold J. Shelley; Discussion of the first case by John Douglas; Discussion of the second case by Edward Peterson; c] Carcinoma of the lower rectum, Harold Brown Keyes; Discussion by William F. MacFee; d] Case illustrating paper on lymphogranuloma venereum, A. W. Martin Marino; e] Case illustrating paper on duodenal obstruction in the new born, Walter Stenson. ¶ Papers of the evening—a] The anorectal aspect of venereal lymphogranuloma, A. W. Martin Marino; Discussion by Frank C. Yeomans; b] Duodenal obstruction in the newborn. A successful operation on a premature twin, Walter Stenson; Discussion by DeWitt Stetten, Jerome Leopold, Edward Donovan. ¶ General discussion.

DECEMBER 7—*Dermatology and Syphilology.* Reading of the minutes. ¶ Presentation of cases—a] Skin and cancer unit of the Post-Graduate Medical School; b] Miscellaneous cases. ¶ Discussion of selected cases. ¶ Executive session.

DECEMBER 9—*New York Meeting of the Section of Pediatrics.* Symposium on tumors of childhood presented by members of the staff of the Memorial Hospital. Presentation of cases—a] A five year cure of a case of osteogenic sarcoma of the calcis, Norman L. Higinbotham; b] Hypertrophy of breast in a child, Joseph Farrow (by invitation); c] A case of hygroma of the neck, Robert L. Brown (by invitation). ¶ Papers of the evening—a] General considerations of cancer in children, Harold W. Dargeon; b] Malignant tumors of soft tissues in infancy and childhood, George T. Pack; c] Diagnosis and treatment of primary bone tumors in children, Bradley L. Coley; d] Malignant tumors of the head and neck in children, Hayes E. Martin; e] Blood and lymph vessel tumors in children, William L. Watson; f] Malignant lymphomatous tumors and leukemia in childhood, Lloyd F. Craver. ¶ Discussion, James Ewing, Frank E. Adair.

DECEMBER 14—*Neurology and Psychiatry.* Papers of the evening—a] The attitude of the psychoneurotic toward scientific contraceptive advice, Jacob H. Friedman; Discussion, Israel Strauss, Clarence P. Oberndorf; b] Physiology of vision and quantitative visual test for

* This was the first of two lectures on the general subject: "The Interactions of the Endocrine and Nervous Systems."

localization of tumors of brain—a preliminary report, Charles A. Elsberg, Hyman Spotnitz (by invitation); Discussion, Selig Hecht, Ph.D., Professor of Biophysics, Columbia University (by invitation); John M. Wheeler; Felix Bernstein (by invitation); Richard Brickner; Hyman Spotnitz (by invitation); c] Observations on motor apraxia, Earl C. Chesher (by invitation); Discussion, Kurt Goldstein (by invitation). ¶ Executive session.

DECEMBER 15—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Presentation of cases—a] An induction motor suction pump for urological drainage, Harold E. Stedman (by invitation); b] A case of hydrocele renis, Stanley R. Woodruff, H. S. Rupert (by invitation). ¶ Paper of the evening—A clinical consideration of simple renal infections in the pregnant woman, Leon Herman, Craig W. Muckle, Philadelphia (by invitation). ¶ Discussion, Henry Dawson Furniss, Harbeck F. Halsted, George F. Hoch, Herbert F. Traut.

DECEMBER 15—*Otolaryngology.* Reading of the minutes. ¶ Presentation of cases—a] Malignant granuloma of the ethmoids, Alfred F. Hocker (by invitation); b] Myxochondroma of the nose in an infant, Gervais W. McAuliffe. ¶ Papers of the evening—a] Laryngo-fissure for removal of intrinsic carcinoma of the larynx (illustrated by colored motion pictures), Arthur Palmer. (All of the foregoing contributions were from the otolaryngological staff of the New York Hospital, Cornell Medical College); b] A short report on the use of a new local anesthetic agent which gives prolonged analgesia, W. Wallace Morrison; Discussion, Alexander F. Lazlo (by invitation), Caesar Hirsch (by invitation); c] Otogenous cerebellar abscess, E. Miles Atkinson (by invitation); Discussion, Marvin F. Jones, J. E. J. King. ¶ General discussion. ¶ Executive session.

DECEMBER 17—*Orthopedic Surgery.* Reading of the minutes. ¶ Papers of the evening—a] The relationship of orthopedic surgery to internal medicine, Harold T. Hyman (25 minutes); b] Subluxation of the cervical vertebrae, Barbara B. Stimson (30 minutes); c] Discussion, Alan DeForest Smith, Paul Swenson (by invitation); d] Resume of eighty operative cases of internal derangement of the knee joint, limited to damage to the semilunar cartilages, William Hadden Irish (25 minutes); e] Demonstration of a correcting spinal brace, John B. Byrne (15 minutes). ¶ Discussion.

DECEMBER 20—*Ophthalmology.* Instructional hour—Diagnostic value of the fundus, Ernest F. Krug. ¶ Slit lamp demonstration, Milton L. Berliner, Girolamo Bonaccolto, Gordon M. Bruce. ¶ Reading of the minutes. ¶ Survey of eye clinics, N. Y. City, Robert R. M. McLaughlin. ¶ Presentation of cases—a] Etiology and treatment of keratoconus, Arthur A. Knapp; b] Contrast media in orbital roentgenography, Murray A. Last. ¶ Paper of the evening—Lymph spaces and lymphatics in and about the orbit, Oscar V. Batson (by invitation).

DECEMBER 21—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] The nature and treatment of heart failure, Paul D. White, Boston (by invitation); Discussion, Lewis Fox Frissell, Henry S. Patterson, Harold J. Stewart; b] The value of the precordial electrocardiogram in coronary artery disease, Francis Clark Wood, Philadelphia (by invitation); Discussion, Arthur M. Master. ¶ General discussion.

DECEMBER 28—*Obstetrics and Gynecology.* Presentation of cases—a] Tuberculous pyonephrosis complicating pregnancy. Nephrectomy, Norman Pleshette (by invitation); Discussion, Seymour F. Wilhelm; b] Postpartum hemorrhage with uterine atony. Hysterectomy, Harry Schneider (by invitation); Discussion, Harbeck Halsted. ¶ Papers of the evening—a] The comparative value of pelvioradiography and clinical pelvimetry in the course and progress of labor,

Samuel J. Scadron, Emanuel Rappaport (by invitation); Discussion, William E. Caldwell, Howard C. Moloy (by invitation), Kyle B. Steele (by invitation), Claude E. Heaton; b] Maternal intracranial hemorrhage complicating labor (with a report of three cases), H. Leo Moskowitz (by invitation); Discussion, Emanuel D. Friedman.

AFFILIATED SOCIETIES

DECEMBER 15—*New York Section of the Society for Experimental Biology and Medicine.* Red cell and reticulocyte counts in guinea pigs following exposure to low pressures, Albert S. Gordon, William Kleinberg (introduced by Harry A. Charipper). ¶ Sensitization and antibody formation after the injection of tubercle bacilli, Jules Freund, J. Casals (by invitation), Elizabeth Page Hosmer (by invitation). ¶ Direct effect of adrenal cortical hormone on blood pressure in shock induced by intestinal manipulation, W. W. Swingle, W. M. Parkins (by invitation), A. R. Taylor (by invitation), H. W. Hays (by invitation). ¶ Relation of carrier state to pneumococcal peritonitis in young children with the nephrotic syndrome, C. M. MacLeod, L. E. Farr (introduced by O. T. Avery). ¶ A simple, inexpensive method for concentrating serum under sterile conditions, William Thalhimer. ¶ Experimental exchange transfusions for reducing azotemia and the experimental use of an artificial kidney for that purpose, William Thalhimer. ¶ The action of parasympathomimetic drugs on sympathetic synapses, Amedeo S. Marrazzi (introduced by I. Greenwald).

DECEMBER 20—*New York Roentgen Society.* Presentation of interesting cases. ¶ Papers of the evening—a] The application of the laminagraph to body section radiography, Sherwood Moore, St. Louis; b] Cine-roentgenography, Maurice Louis Van de Maele, Brussels, Belgium; Presentation by William H. Stewart. ¶ Executive session.

DECEMBER 23—*New York Pathological Society in affiliation with The New York Academy of Medicine.* Case reports—a] Generalized arteriosclerosis with hypertrophy of the media and atypical hyaline degeneration affecting the intima, media and adventitia, Charles T. Olcott; b] Epidermoid carcinoma of the breast, N. Chandler Foot. ¶ Papers of the evening—a] Studies on experimental hypertension, Charles G. Child (by invitation); b] A study of myocardial hypertrophy of uncertain etiology in congestive heart failure. Particular reference to the role of antecedent hypertension, Bernard I. Kaplan (by invitation), Eugene Clark, Clarence E. de la Chapelle. ¶ Executive session.

THE JOSEPH COLLINS LECTURES

The first and second lectures were delivered at the Academy on December 2 and December 8, 1937, at 8:30 o'clock by Dr. Charles R. Stockard, Professor of Anatomy, Cornell University Medical College, on the general subject, "The Interactions of the Endocrine and the Nervous Systems." ¶ Lecture No. 1, Thursday evening, December 2, "The Mechanism Operating the Body as an Integrated Unit." (This lecture also constituted the Anniversary Discourse of the Academy). ¶ Lecture No. 2, Wednesday evening, December 8, "Endocrine Changes and Modifications in Function and Behavior." Physicians and the public were invited to attend the Lectures.